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Mismatch Negativity: No Difference Between Treatment-Naive Alcoholics and Controls

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Background: Several studies have examined the mismatch negativity (MMN) evoked potential as a measure of a brain inhibitory deficit in alcoholics or those at risk for alcoholism. This study examined MMN in actively drinking treatment-naive alcohol-dependent individuals. This study examined the association of MMN with risk factors for alcoholism, postalcohol withdrawal hyperexcitability, and alcohol use variables.

Methods: Electroencephalograms were gathered on 84 subjects (42 controls and 42 treatment-naive alcohol-dependent individuals) during a nonattending MMN experiment. Alcoholism family history density, the number of externalizing disorder symptoms, and psychological indices of deviance proneness served as measures of risk factors associated with the vulnerability to alcoholism. Alcohol use variables were used as measures of alcoholism severity.

Results: There were no differences in the MMN integral, amplitude, or latency between control and treatment-naive alcohol-dependent subjects. There also were no significant associations of MMN measures with any of the measures of alcoholism vulnerability, with any of the alcohol use variables, or with the prevalence or severity of symptoms of postalcohol withdrawal hyperexcitability.

Conclusions: Although there is a strong association between alcohol abuse and symptoms of disinhibition and deviance proneness, the MMN response does not offer any direct physiological evidence of this phenomenon.

Key Words: Mismatch Negativity, Alcoholism, EEG, Family History Density, Externalizing Symptoms.

SEVERAL STUDIES HAVE indicated that the brains of alcoholics process stimuli differently than those of nonalcoholics. This has been demonstrated in the areas of target detection (Polich et al., 1994), orienting (Fein et al., 1995), aspects of inhibitory function (Ahveninen et al., 2000), response to reward and punishment (Bechara et al., 2001; Lejoyeux et al., 1998, 1999), and behavioral disinhibition (LeMarquand et al., 1999). These differences may be a consequence of the alcohol use itself, or they may reflect differences in biological vulnerabilities that predispose an individual to alcoholism (Begleiter et al., 1984). Predisposition to alcoholism has been linked to several factors, including a family history of alcoholism, the presence of conduct disorder and antisocial personality disorder, and the presence of disinhibited personality traits (Chassin et al., 1999a,b; Finn et al., 2000, 2002). Furthermore, current theories propose that disinhibition is a fundamental mediator of the inherited predisposition toward alcohol dependency (Begleiter and Porjesz, 1999; Cloninger, 1987; Sher et al., 1991; Tartar et al., 1985). Many data suggest that early-onset alcoholism is not a unique problem but is related to a cluster of disinhibited traits. It has been proposed that behavioral phenomena such as psychopathy, antisocial and impulsive traits, and alcoholism should be viewed as variable expressions of a generalized disinhibitory complex (Gorenstein and Newman, 1980).

Mismatch negativity (MMN) is a preattentive brain response to changes in auditory stimulation and has been proposed in recent studies as a measure of the brain inhibitory deficit associated with alcoholism or the vulnerability to alcoholism (Kathmann et al., 1995; Zhang et al., 2001). Lack of inhibition, or even disinhibition, is thought to be reflected by an increase in MMN amplitudes seen in individuals who are at high risk for alcoholism (Zhang et al., 2001). If increased MMN amplitude is associated with alcoholism or a predisposition to alcoholism, then it should be present in treatment-naive (TxN) alcohol-dependent individuals, and it should covary with the factors that may predispose an individual to alcoholism, such as a family history of alcoholism, symptoms of conduct and antisocial personality disorder, and disinhibited personality traits (Finn et al., 2002).

We recently published a study (Fein et al., 2004) on long-term abstinent alcoholics that examined the effects of prior alcohol abuse, abstinence duration, and alcoholism family history density (FHD) on MMN measures. The MMN amplitude was assessed in adult long-term abstinent

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Table 1. Characteristics of Participant Groups

Variable	Treatment naive		Control		Effect size (%)		
	Male (n = 23)	Female (n = 19)	Male (n = 23)	Female (n = 19)	Group	Gender	Group × Gender
Age (years)	33.2 ± 8.7	30.0 ± 6.7	33.1 ± 8.6	30.1 ± 3.7	0.0	3.8	0.0
Years of education	16.4 ± 1.6	16.1 ± 1.2	16.1 ± 2.4	16.5 ± 1.2	0.0	0.0	1.2
Family history density score	0.36 ± 0.40	0.63 ± 0.54	0.29 ± 0.37	0.32 ± 0.41	4.1	2.8	2.0
Alcohol use variables							
Duration of active drinking (months)	210.2 ± 107.9	176.7 ± 80.8	150.1 ± 104.3	125.9 ± 99.7	7.5[a]	2.0	0.0
Average lifetime drinking dose (standard drinks/month)	99.3 ± 38.1	58.5 ± 21.1	8.5 ± 8.3	4.7 ± 4.0	66.0[a]	5.9***	4.1[a]
Duration of peak drinking (months)	61.8 ± 61.3	59.5 ± 56.5	87.4 ± 127.6	32.3 ± 23.3	0.0	3.2	2.3
Peak drinking dose (standard drinks/month)	170 ± 73.3	98.3 ± 40.4	19.7 ± 18.1	12.4 ± 10.2	59.4[a]	6.3***	4.1[a]
Deviance proneness personality measures							
California Psychological Inventory—Socialization scale	32.3 ± 5.1	31.5 ± 5.8	36.3 ± 4.1	37.7 ± 4.3	21.7***	0.0	1.1
Minnesota Multiphasic Personality Inventory—Pd scale	21.2 ± 5.8	21.4 ± 5.1	17.7 ± 3.1	19.2 ± 4.6	8.8**	0.7	0.5
Externalizing symptoms (n)[b]	12.6 ± 8.0	7.4 ± 7.4	7.2 ± 6.8	4.2 ± 3.0	9.4**	8.1**	0.6

Data are mean ± SD unless otherwise noted.
[a] Significance levels for group comparisons of alcohol use variables are not valid because alcohol use was part of the group selection criteria.
[b] Sum of antisocial personality disorder and conduct disorder symptoms from the DIS.
Effect is significant: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

alcoholics and nonalcoholic controls (n = 76). The study found that MMN measures were not associated with alcohol use, familial alcoholism vulnerability, externalizing symptom counts (antisocial personality and conduct disorder), or psychological measures of deviance proneness (psychopathic deviance or socialization). That study, however, left open the question of the effects on the MMN measures of both active alcohol abuse and of alcohol withdrawal–associated central nervous system hyperexcitability (Ahveninen et al., 2000; Alling et al., 1982).

This study examined MMN in actively drinking, TxN alcohol-dependent individuals compared with light-drinking or nondrinking controls. The study addresses the effects on MMN of active abusive drinking, alcoholism vulnerability (including deviance proneness and the presence and history of externalizing symptoms), and post-alcohol withdrawal hyperexcitability (PAWH).

MATERIALS AND METHODS

Participants

A total of 84 participants were recruited from the San Francisco Bay area via postings of community-based flyers, advertisements on an Internet site, and referrals from participants. The TxN alcohol-dependent sample was recruited by advertising for "heavy social drinkers" or "men and women who have a high tolerance for alcohol." Inclusion criteria for the TxN group was that they currently met DSM-IV-R (American Psychiatric Association, 2000) criteria for alcohol dependence and that they had never sought treatment. In fact, none of the TxN subjects labeled themselves as alcoholic, and we never used the word *alcoholism* in our advertisements or in their assessment procedures. This was done so as not to deter possible participants from entering the study. Almost by definition, TxN alcohol-dependent individuals are in denial about their alcohol problems, and we did not want to directly confront that denial and risk creating a hostile environment. However, when a subject did acknowledge his or her problems with alcohol and ask for help, information was always provided as to where that individual could best receive possible treatment (including a referral to Alcoholics Anonymous). The study sample consisted of 42 TxN subjects (23 men and 19 women) and gender- and age-matched controls. Table 1 presents subject demographics, alcoholism FHD, alcohol use variables, the number of externalizing disorder symptoms, and two personality measures of deviance proneness. Inclusion criteria for the control group was a lifetime drinking average of fewer than 30 alcohol-containing drinks per month and having never exceeded 60 drinks per month.

Assessment

A computerized version of the Diagnostic Interview Schedule (DIS) (Robins et al., 1998) was used to establish psychiatric and substance abuse diagnoses. Exclusion criteria for both groups were (1) a history or presence of an axis I diagnosis on the DIS; (2) a history of drug dependence other than caffeine or nicotine; (3) a significant history of head trauma or cranial surgery; (4) a history of diabetes, stroke, hypertension, or other significant neurological disease that required medical intervention; (5) laboratory evidence of hepatic disease; (6) clinical evidence of Wernicke-Korsakoff syndrome; or (7) current substance abuse other than alcohol (aside from caffeine or nicotine).

Procedures

All participants were informed of the study's procedures and signed a consent form before their participation. All of the procedures performed during the experiments had received approval from the institutional review board. There were four sessions that varied in length from 1 to 3 hr. The sessions involved clinical, neuropsychological, electrophysiological, and neuroimaging assessment. The clinical interview included a review of the participant's medical history and a detailed assessment of the individual's alcohol use history, including a history of withdrawal symptoms. After the first day, all participants underwent a blood draw to exclude individuals with hepatic disease. The electroencephalogram (EEG) stud-

ies took place on the third visit. This study examined only the MMN experiment in conjunction with measures of the density of the family history of alcoholism, externalizing symptom counts, deviance proneness measures, and alcohol use variables. All subjects were asked to abstain from drinking alcohol for 24 hr before each session, and a breathalyzer test was administered before each session to ensure their compliance with that request. A breathalyzer score of 0.000 was required to continue with the session, and no individuals in this study failed the breathalyzer test. All of the participants were paid for their time and travel expenses and were given a completion bonus after finishing the entire study.

Measures

Alcohol Use Variables. Alcohol use variables were defined according to the subject's responses to the lifetime drinking history questionnaire (Sobell et al., 1988), which was designed to capture relevant features of consumption behavior. A standard drink was defined as 12 oz of beer, 1.5 oz of liquor, or 5 oz of wine. Alcohol lifetime duration was defined as the total number of months in which the subject was actively drinking. The lifetime average dose was defined as the average number of standard drinks per month. The peak use variables indicated maximum levels of consumption. Peak dose was defined as the maximum monthly consumption of standard alcohol drinks, and the peak duration was defined as the total number of months (possibly discontinuous) that a participant engaged in this peak use. Separate lifetime use histories, using the same method as the lifetime drinking history, were gathered for all other drugs (except caffeine and nicotine) used more than experimentally to determine whether a subject met inclusion/exclusion criteria.

Familial Alcoholism Risk. The Family Drinking History Questionnaire, which was based on the Family Tree Questionnaire (Mann et al., 1985), assessed the density of the participants' family history of alcoholism. The Family Drinking History Questionnaire was scored, and assignment into family history–positive and family history–negative groups was determined according to the methods presented by Stoltenberg et al. (1998) for FHD. Biological parents who were identified by the participant as problem drinkers were given a score of 0.50. Grandparents who were identified as problem drinkers were given a score of 0.25; no other relatives were included in the final score. The highest FHD score possible is 2, and the lowest is 0. Participants who scored 0.50 and above were placed in the family history–positive group, and those who scored less than 0.50 were placed in the family history–negative group.

Withdrawal Symptoms. PAWH was measured with a self-report questionnaire on which subjects ($n = 30$) estimated (on a 0- to 10-point scale) the frequency of and distress caused by physical and psychological symptoms experienced during alcohol withdrawal. For the frequency estimate, 0 meant never, 1 corresponded to 10% of the times one ceased drinking, and a 10 indicated that symptom was experienced 100% of the time that one ceased drinking. For the degree of distress caused by the presence of the symptom, 0 meant not at all distressing, 5 meant somewhat distressing, and 10 meant "unbearable." The symptoms were compiled from the DIS (Robins et al., 1998), the Alcohol Dependence Scale (Skinner and Allen, 1982), and Semi-Structured Assessment for the Genetics of Alcoholism interviews (Bucholz et al., 1994). We computed the average frequency and intensity over the following eight symptoms (for the TxN group only) that measure PAWH: (1) shakes (hands tremble; shakes inside); (2) feel tense, nervous, or anxious; (3) feel fidgety or restless; (4) have trouble concentrating; (5) heart pounds or beats rapidly; (6) feel hypersensitive to stimuli (e.g., light, sound, and touch); (7) have difficulty sleeping; and (8) have memory problems.

Disinhibitory Symptoms and Traits. Externalizing disorder symptoms were measured by a total count of the symptoms for conduct disorder and antisocial personality from the DIS (Robins et al., 1998). Personality traits of deviance proneness were assessed with the Psychopathic Deviance (Pd) scale of the Minnesota Multiphasic Personality Inventory (MMPI)-2 (Hathaway, 1989) and the Socialization scale of the California Psychological Inventory (CPI). These measures have been consistently associated with alcoholism risk and behavioral disinhibition (Finn et al., 2000, 2002).

EEG/MMN Measures. The EEG was gathered on the participants' third visit to the laboratory. The participant was seated in a small, sound-attenuated room containing a computer monitor, a response box, EEG amplifier, and other relevant laboratory equipment. Over time, the laboratory progressed from 40-channel to 64-channel EEG recordings. Data were gathered either with the NuAmp 40-channel single-ended amplifier system or the SynAmps2 64-channel single-ended amplifier system (both manufactured by Neuroscan, Inc., El Paso, TX). The ground was positioned 4 cm above the nasion for participants with the 40-channel cap and 8 cm above the nasion for those with the 64-channel cap. All of the recordings were referenced to the right ear. The analysis reported here is restricted to the AFz, Fz, FCz, and Cz channels, which were recorded for all subjects. Electrodes were placed above and below the left eye to monitor blinks and eye movements. The NuAmps amplifier had a fixed input range of ± 130 mV with 22-bit resolution and had a resolution of 0.062 μV. The SynAmps2 amplifier had an input range of ± 333 mV with 24-bit resolution and a resolution of 0.040 μV. Recordings did not begin until all impedances were less than 10 kΩ. Eleven EEG experiments were performed; MMN was the eighth experiment (approximately 50 min from the onset of the experiments).

Mismatch Negativity. For the first 38 participants (TxN, $n = 11$; controls, $n = 27$), the mismatch experiment involved the presentation of 400 stimuli: 350 standard tones and 50 mismatch tones, with the mismatch tone presented pseudorandomly in one eighth of the trials. We then increased the number of stimuli for the last 46 participants (TxN, $n = 31$; controls, $n = 15$) to 500 stimuli (440 standard tones and 60 mismatch tones). The stimuli had a duration of 100 msec, with a 600-msec delay between stimuli and a stimulus intensity of 60 dB. Subjects were randomized as to whether the mismatch tone was the low-frequency (500 Hz) or the high-frequency (2000 Hz) tone. Before the experiment began, the participant was asked to choose something to read from a collection of books and magazines in the laboratory. As the subject became focused on the reading, the technician started the experiment. All data reduction (filtering, epoching, and artifact rejection) was performed offline.

All stimuli were presented by using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA). The EEG data were acquired by using Scan 4.2 (Neuroscan, Inc.) for the participants run on the NuAmps system and Scan 4.3 (Neuroscan, Inc.) for the participants run on the SynAmps2 system. E-Prime and Scan were run on two separate computers. The two computer systems were connected such that for each stimulus, the E-Prime computer sent out an appropriate signal (4–5 msec after the stimulus event) to the Scan computer indicating the type of stimulus so that the information could be integrated into the continuous data recording on the Scan computer. The timing of the E-Prime computer/Scan computer interface was verified with an oscilloscope, and 4 msec was subtracted for all Scan timings so that events were accurate to within 1 msec.

Data Analysis

The continuous raw data were processed offline by using the Edit software in Scan 4.3 (Neuroscan, Inc.). The first step in processing the data involved computing the vertical eye movement channel by taking the difference between the recordings above versus below the left eye. This was needed only for the 40-channel recordings, because the 64-channel system had a number of high-level differential inputs on which the vertical left eye movement was directly recorded. The files were then epoched from 100 msec before to 496 msec after the stimulus events. Epochs with eye movements or blinks exceeding ± 75 μV were excluded. Only subjects with 30 or more artifact-free mismatch epochs were included in the final analysis. The data were then bandpass-filtered from 0.5 to 15 Hz (at 48 dB per octave; zero phase shift). Average mismatch and standard responses were computed, as was the difference between the mismatch and the standard. The area under the curve of the mismatch minus the standard response was then integrated from 100 to 192 msec as the measure of MMN. The amplitude and latency of the MMN was measured from the trough of the MMN difference wave. The MMN measurements follow the

methods used by Zhang et al. (2001). The analysis presented below was restricted to AFz, Fz, FCz, and Cz recordings. The data were analyzed with SAS (SAS Institute, Cary, NC). The amplitude, latency, and area data were analyzed by analysis of covariance, which was performed by using the general linear model procedure implemented in SAS, with group, gender, and interaction effects included. The data were analyzed both without baseline correction and after correcting for the baseline recorded from the 100-msec prestimulus. The association of the MMN measures with alcoholism risk factors and alcohol use variables were analyzed by using Spearman correlations within and across groups. Spearman correlations were also used to analyze the association between MMN measures and PAWH.

RESULTS

The TxN sample had a trend toward a greater alcoholism FHD than controls [$F(1,80) = 3.64$; $p = 0.06$]. The TxN sample differed significantly from the control sample on the CPI Socialization scale, the MMPI Pd scale, and the number of externalizing disorder symptoms. Group membership accounted for 21.7% of the variance on the CPI Socialization scale [$F(1,80) = 22.49$; $p < 0.0001$], with no gender or group × gender effects. The MMPI Pd scale also yielded a significant group membership effect that accounted for 8.8% of the variance [$F(1,80) = 7.79$; $p < 0.01$], with no gender or group × gender effects. There were significant group and gender effects for the externalizing disorder symptom counts, with group membership accounting for 9.4% of the variance [$F(1,80) = 9.18$; $p < 0.01$] and gender accounting for 8.1% of the variance [$F(1,80) = 7.88$; $p < 0.01$]. Additionally, gender accounted for 5.9% of the variance of the average lifetime drinking dose [$F(1,80) = 19.8$; $p < 0.0001$] and 6.3% of the variance of peak drinking dose [$F(1,80) = 16.59$; $p < 0.0001$].

Figure 1 presents the baseline corrected group average mismatch and standard responses at AFz, Fz, FCz, and Cz, along with the MMN integrals. It illustrates a strong MMN component at all electrodes for both groups. Analysis of covariance did not reveal any significant MMN group, gender, or group × gender interaction effects for latency, amplitude, or area at AFz, Fz, FCz, or Cz (for both the baseline-corrected and non–baseline-corrected data). For both baseline-corrected and non–baseline-corrected data, group accounted for less than 0.8% of the variance at each electrode site (all p's > 0.40).

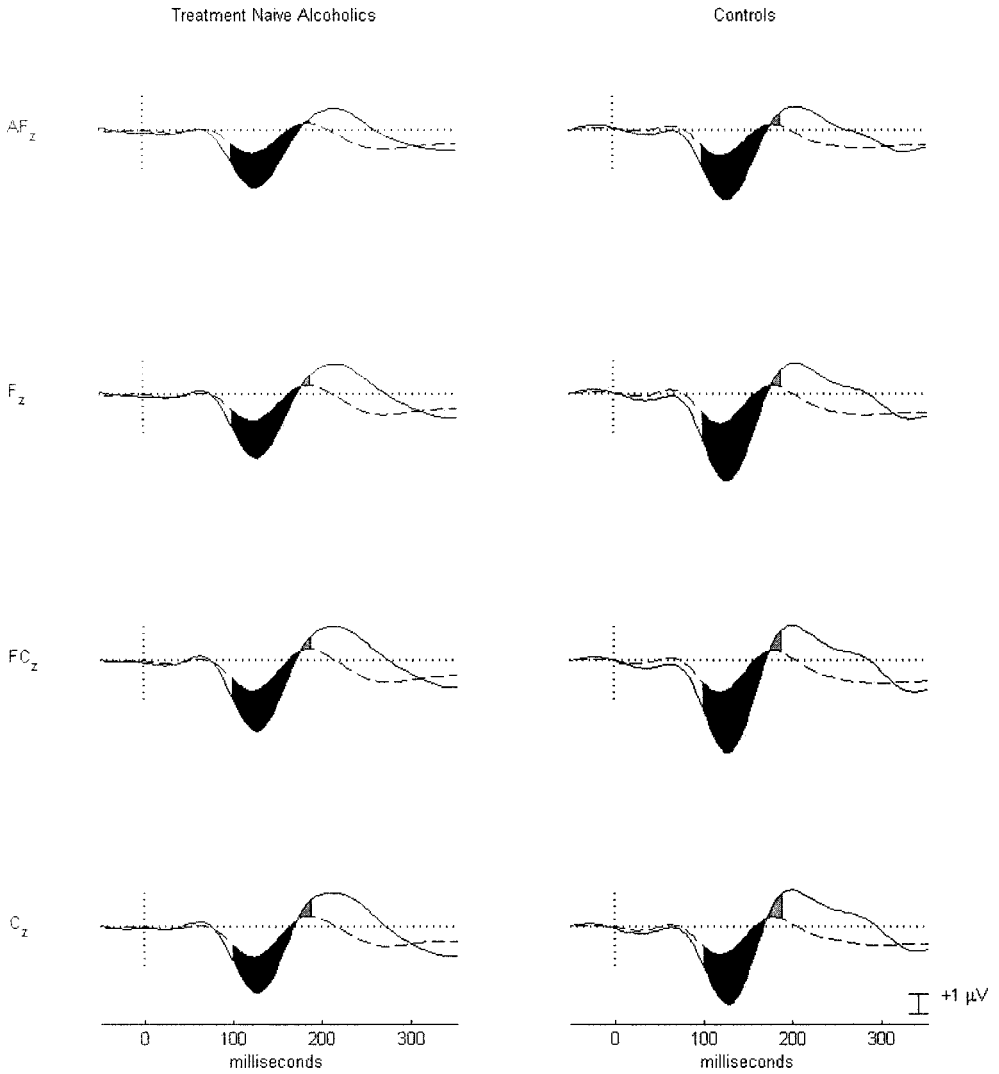

Fig. 1. Group average event-related potential responses to the standard (dashed lines) and mismatch (solid lines) stimuli. Data have been baseline-corrected for activity from the 100-msec prestimulus interval. The group average MMN integrals from 100 to 190 msec are displayed as the filled-in areas between the standard and mismatch curves. No group difference was observed at any of the electrodes (all p's > 0.40)

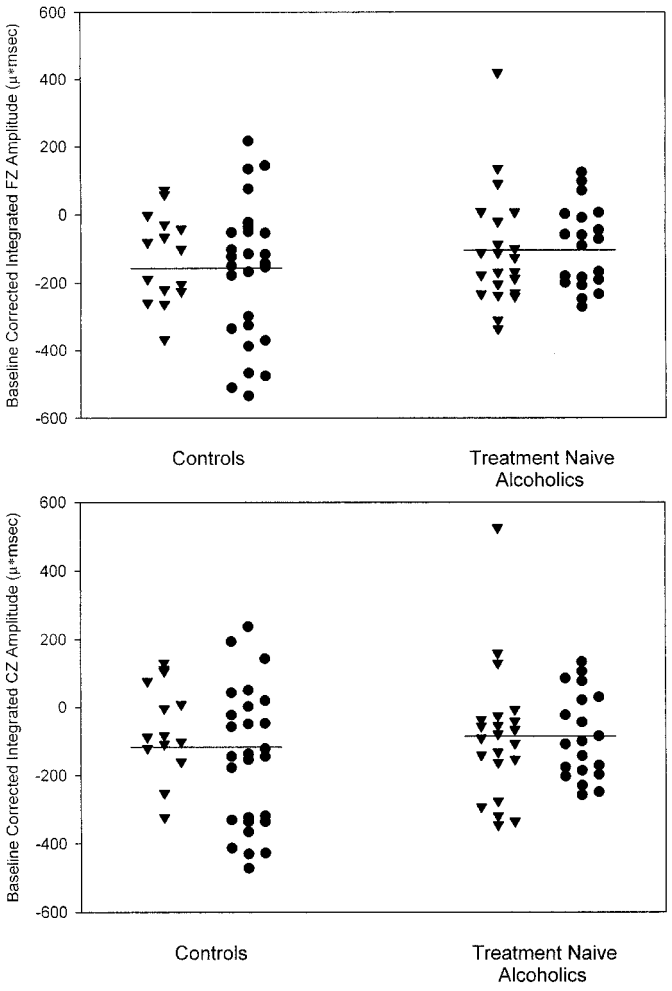

Fig. 2. Scatterplots of the MMN integrals for the baseline-corrected data. Within each group, family history–positive subjects are represented by triangles, and family history–negative subjects are represented by circles. The averages for each group are represented by horizontal lines. The figure illustrates that the MMN integral does not differ between the subject groups or between family history–positive and family history–negative subjects (all p's > 0.12).

No significant Spearman correlations were observed within or across groups of MMN area (integral) with FHD scores, the number of externalizing symptoms, deviance proneness personality scores, or alcohol use variables. Figure 2 presents the raw data showing no group difference in MMN integrated amplitude and illustrates the lack of association between family history status and MMN integrated amplitude. We also examined the association between MMN area and the average frequency and intensity of the eight symptoms of PAWH. The analysis was limited to the TxN subjects who had completed the questionnaire that quantified their withdrawal symptoms ($n = 30$). The questionnaire used a 0-to 10-point scale, and the average frequency across all of withdrawal symptoms was 3.3, with an SD of 1.8 and an average intensity of 4.2 with an SD of 1.7. Thus, on average, subjects experienced withdrawal symptoms 33% of the time that they ceased drinking, and on average the symptoms distressed them "somewhat" (corresponding to a rating of 4). There were no significant correlations, suggesting that PAWH did not affect MMN area (all $|r$'s$| < 0.11$ and p's > 0.58 for frequency; all $|r$'s$| < 0.25$ and p's > 0.21 for intensity).

DISCUSSION

The MMN paradigm used in this study and in our prior study (Fein et al., 2004) was very similar to that of Zhang et al. (2001), which detected an increased MMN response in individuals at a high risk for alcoholism. In the prior study, a strong MMN response was observed, but it did not differ between groups. The goal of this study was to extend our prior results to address MMN differences in active alcoholics and in the presence of PAWH. We did not find any MMN differences in our active alcoholics compared with age- and gender-matched controls, nor did we find any association of the MMN response with indices of the frequency or severity of PAWH. The MMN responses we observed in this study not only mirror those of our last study, but also look quite similar to MMN responses observed by others (Jaaskelainen et al., 1996; Zhang et al., 2001).

We acknowledge that there are slight differences between the MMN paradigm we used and that used by Zhang et al. (2001). The largest difference was in the reference used; Zhang et al. (2001) used a nasion reference, whereas we used a right earlobe reference. Other minor differences exist in the exact stimulus characteristics used, online versus offline artifact rejection, and input impedances. Regarding the choice of reference, we note that the right earlobe or right mastoid has been used in many of the MMN alcoholism studies and that the MMN responses seem comparable across studies. Moreover, we contend that if the difference in findings between our studies and that of Zhang et al. are a result of the slight differences in method and hardware, then that, in itself, is evidence that the association of MMN amplitude with alcoholism is not robust.

Although the TxN group exhibited a trend toward a greater FHD of alcoholism than controls, our sample had less of a family history of alcoholism loading than either our earlier study (Fein et al., 2004) or that of Zhang et al. (2001). However, we did not find any significant correlation between the MMN area and FHD, which fails to support the hypothesis that the MMN is a marker for the predisposition to alcoholism.

In our previous study in long-term abstinent, treated alcoholics, we found a strong group difference between alcoholics and controls in deviance proneness and in externalizing symptoms. In this study, the groups differed on these measures, but not as strongly as they did in the prior study. We believe that this was due to the greater severity of alcoholism in the treated versus TxN samples (Fein and Landman, 2004). Nonetheless, in both studies we failed to find any association between MMN measures and measures of deviance proneness or externalizing symptoms.

Although there is a strong association between alcohol abuse and symptoms of disinhibition and deviance proneness, the MMN response does not offer any direct physiological evidence of this phenomenon. Thus, the findings presented in this article and our previous article (Fein et al., 2004) bring into question the degree to which MMN indicates disinhibition in alcoholics.

We acknowledge that our studies do not close the door on any association of MMN amplitude with alcoholism. Both of our studies excluded individuals with a lifetime diagnosis of antisocial personality disorder or conduct disorder. It is possible that MMN is abnormal in alcoholics with much more severe externalizing symptoms or deviance proneness than were the subject of our studies. Moreover, our sampling did not select for individuals who were experiencing severe withdrawal from alcohol; thus, we cannot say that PAWH is not associated with an increased MMN response when that withdrawal is more severe. Although our sample might not demonstrate the entire range of alcoholism severity and comorbidity, we believe that our sample is more representative of alcoholics in the general population, because only approximately 10% of individuals who meet criteria for alcohol dependence or abuse ever seek treatment (Grant, 1994).

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